HED DOC. NO. 013584

21-JULY-1999

MEMORANDUM

SUBJECT: ***PHOSMET*** **-** Report of the FQPA Safety Factor Committee

The FQPA safety factor and the basis and rationale for the recommendation in this report supercedes that previously reported for phosmet in the FQPA SAFETY FACTOR RECOMMENDATIONS FOR THE ORGANOPHOSPHATES dated August 6, 1998.

FROM: Brenda Tarplee, Executive Secretary
FQPA Safety Factor Committee
Health Effects Division (7509C)

THROUGH: Ed Zager, Chairman
FQPA Safety Factor Committee
Health Effects Division (7509C)

TO: Christina Swartz, Risk Assessor
Reregistration Branch 1
Health Effects Division (7509C)

PC Code: 059201

The FQPA Safety Factor Committee met on July 12, 1999 to reevaluate the hazard and exposure data for phosmet considering recently reviewed toxicity studies. The FQPA safety factor and the basis and rationale for the recommendation in this report supercedes that previously reported for phosmet in the *FQPA SAFETY FACTOR RECOMMENDATIONS FOR THE ORGANOPHOSPHATES* dated August 6, 1998.

I. HAZARD ASSESSMENT

A. Adequacy of Toxicology Database

On July 8, 1999, the HIARC reviewed the recently submitted acute and subchronic neurotoxicity studies with phosmet in rats and NTE data for the hen study, which were previously identified as data gaps. The HIARC determined that these studies were acceptable and therefore, there are no data gaps for the standard Subdivision F Guideline requirements for a food-use chemical by 40 CFR Part 158.

At this meeting, however, the HIARC determined that a developmental neurotoxicity study in rats is required due to the evidence of neuropathology in the subchronic neurotoxicity study in rats that can not be discounted. The neuropathology observed in this study was described as minimal digestion chambers in sciatic nerves of 3/5 male rats at the high dose. The Committee members were not sure of the significance of these lesions at the time of the HIARC meeting and in the interest of time as well as to be protective, the HIARC recommended a DNT be required.

On July 15, 1999, Phosmet was brought back to the HIARC to re-evaluate the neuropathology observed in the Subchronic Neurotoxicity Study in rats. Dave Eisenbrandt, pathologist with Global Toxicology Dow AgroSciences joined the Committee via telephone to characterize the digestion chambers observed in sciatic nerve fiber in this study. In summary, these lesions occur spontaneously and are very common in all strains of rats. Based on the information provided and the fact that neuropathology was not observed in any other studies, **the HIARC revoked the requirement a developmental neurotoxicity study in rats.**

B. Evaluation of Neurotoxicity

Phosmet is a neurotoxic organophosphate. There is evidence of neurotoxicity exhibited as tremors, subdued behavior, shaking, unsteady gait, and convulsions in the developmental toxicity and 2-generation reproduction studies in rats, the developmental toxicity study in rabbits, and the carcinogenicity study in mice. Brain cholinesterase inhibition has been observed in every study in which it has been measured and in every species tested (rat, mouse, and dog).

In the recently-submitted subchronic neurotoxicity study in rats, an increase in the neuropathological changes (characterized by digestion chamber in the sciatic and peroneal nerves) was seen in high dose male rats (perfuse). When compared to concurrent controls, high-dose male rats exhibited digestion chambers (minimal) of the sciatic nerve [3/5 (60%) treated vs 0/5 controls] and peroneal nerve (1/5 treated vs 0/5 controls). Therefore, it could not be ruled out that this was a treatment-related effect (MRID 44811801).

C. Determination of Susceptibility

Prenatal developmental toxicity studies in rats and rabbits provided no indication of increased susceptibility of rat or rabbit fetuses to *in utero* exposure to phosmet. There was no indication of increased susceptibility in the offspring as compared to parental animals in the two generation reproduction study. In these studies, effects in the fetuses/offspring were observed only at or above treatment levels which resulted in evidence of parental toxicity.

D. Determination of Developmental Neurotoxicity Study

The HIARC determined that a developmental neurotoxicity study in rats is not required for phosmet.

E. Data Gaps

None.

II. EXPOSURE ASSESSMENT AND RISK CHARACTERIZATION

A. Dietary Exposure Considerations

Permanent tolerances have been established for the combined residues of the insecticide phosmet and its oxygen analog in/on a variety of raw agricultural commodities at levels ranging from 0.1 ppm (cottonseed, nuts, potatoes) to 40 ppm (alfalfa) [40 CFR §180.261].

Phosmet is used on (or residues can transfer to) many foods which are highly consumed by infants and children, including apples, citrus fruits, peaches, pears, peas, and meats (1993 NAS report, Pesticides in the Diets of Infants and Children).

Residue data sources available for phosmet include: field trial data; processing studies; Pesticide Data Program (PDP) monitoring data; and FDA surveillance data. The Biological and Economic Analysis Division (BEAD) has provided an updated Quantitative Usage Analysis (6/99 QUA) with weighted average and estimated maximum percent of crop treated (%CT) data as well as the average application rates and number of applications per year.

Some processing studies indicate that phosmet residues will be reduced through washing and peeling (peach and apple processing studies), and residues are reduced in processing fruits into juices (apples, grapes). Phosmet is not considered to be a systemic insecticide.

With the exception of potatoes and nuts, all phosmet tolerances are based on detectable residues. Extensive PDP and FDA monitoring data are available to refine the exposure assessment. Residues were detected in approximately 6% of apples, 0.5% of apple juice, 20% of fresh peaches and 0% of canned peaches (PDP). Both composite (27% detects) and single serving (47.2% detects) pear data are available (PDP). Phosmet residues were not detected in 202 milk samples.

Dietary food exposure analyses were performed to estimate the acute and chronic dietary risk for phosmet using the Dietary Exposure Evaluation Model (DEEM). DEEM combines pesticide residue data with food consumption data to estimate dietary (food only) exposure. Both the chronic and acute analyses are highly refined using anticipated residue estimates based on available monitoring data and field and processing studies, as well as percent crop treated and application information. In addition, the acute analysis used the decompositing method developed by HED to estimate the level of residues expected in single servings of foods. The result is a more realistic estimate of the dietary exposure expected from the application of phosmet to food commodities.

B. Drinking Water Exposure Considerations

The environmental fate data base for phosmet is complete. Based on the laboratory and field studies conducted, it does not appear that phosmet or phosmet oxon will pose a

significant threat to ground water resources. Phosmet is moderately mobility however, terrestrial field dissipation studies suggest that the parent compound does not persist long enough to exhibit substantial leaching. Phosmet can contaminate surface water via runoff if runoff-producing rain events occur within the first few days to weeks post application.

A small amount of ground water monitoring data has been collected and reported to the STORET system and the *Pesticide in Ground Water Database* (A Compilation of Monitoring Studies: 1971-1991 National Summary; Published in September 1992) on the occurrence of phosmet between 1981 and 1990.

The screening model for ground water, SCI-GROW, was used to estimate the "maximum" groundwater concentrations resulting from the application of a phosmet to crops. SCI-GROW is based on the fate properties of the pesticide, the annual application rate, and the existing body of data from small-scale ground water monitoring studies. The model assumes that the pesticide is applied at its maximum rate in areas where the groundwater is particularly vulnerable to contamination. In most cases, a considerable portion of any use area will have ground water that is less vulnerable to contamination than the areas used to derive the SCI-GROW estimates. As such, the estimated maximum concentration derived using SCI-GROW should be considered a high-end to bounding estimate of "acute" exposure.

Surface water monitoring data for phosmet are extremely limited (several counties among three states) and therefore, cannot be used for a definitive exposure and risk assessment. Although the levels found suggest that phosmet does not exceed concentrations above the very low ug/l range, the reported incidences were not correlated with use patterns, were collected randomly throughout the year, and were of insufficient numbers to make definitive statements as to extent of contamination of surface waters.

At the time of this meeting, Tier II surface water Estimated Environmental Concentrations were being re-calculated using the updated Quantitative Usage Analysis (6/99 QUA) for phosmet with PRZM3.1 to simulate the agricultural field and EXAMS 2.97.5 for fate and transport in surface water.

C. Residential Exposure Considerations

Phosmet is currently registered for residential use on ornamental shrubs and small trees, vegetable and flower gardens, and for pet care uses.

No chemical-specific data for phosmet are available to assess post-application exposure to infants and children following outdoor residential applications. Therefore, the DRAFT Standard Operating Procedures (SOPs) for Residential Exposure Assessments will be used for these post-application exposure scenarios using surrogate data. The DRAFT SOPs normally rely on one or more upper-percentile assumptions and are intended to represent Tier 1 screening assessments.

III. SAFETY FACTOR RECOMMENDATION AND RATIONALE

A. Recommendation of the Factor

The Committee recommended that the FQPA safety factor for protection of infants and children (as required by FQPA) should be **removed** (1x) for phosmet.

B. Rationale for Selection of the FQPA Safety Factor

The Committee recommended that the **FQPA safety factor** be **removed** because:

- The toxicology data base for phosmet is now complete;
- There was no evidence of developmental effects being produced in fetuses at lower doses as compared to maternal animals nor was there evidence of an increase in severity of effects at or below maternally toxic doses following *in utero* exposure in the prenatal developmental toxicity studies in rats and rabbits;
- In the pre/post natal two-generation reproduction study in rats, there was no evidence of enhanced susceptibility in pups when compared to parental animals (i.e., effects noted in offspring occurred at maternally toxic doses or higher);
- There was no evidence of abnormalities in the development of the fetal nervous system in the pre/post natal studies submitted to the Agency; and
- Adequate actual data, surrogate data, and/or modeling outputs are available to satisfactorily assess dietary (food) and residential exposure and to provide a screening level drinking water exposure assessment.